J. Am. Chem. Soc. **1998,** *120,* 5345−5346

Carbozincation of Enynes Catalyzed by Titanium(IV) Alkoxides and Alkylmagnesium Derivatives[†]

Jean-Luc Montchamp and Ei-ichi Negishi*

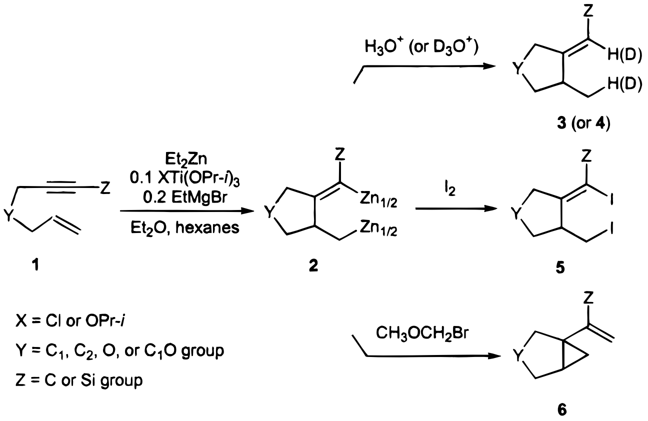
Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received November 10, 1997

We report herein that a novel trimetallic reagent system consisting of Et_2Zn (Aldrich or Strem) $XTi(OPr^i)_3$ (0.1 equiv), where X is Cl or OPr^i, and an alkylmagnesium halide (0.2 equiv), e.g., EtMgBr and Pr^iMgCl, reacts with various enynes (**1**) to produce the corresponding cyclic organozinc derivatives **2**. Protonolysis, deuteriolysis, and iodinolysis of **2** provide the corresponding derivatives **3**−**5**, while treatment of **2** with CH_3OCH_2Br (1.1 equiv relative to an enyne) provides in good yields the corresponding 1-alkenylbicyclo[*n*.1.0]alkanes **6**, where *n* is 3 or 4 (Scheme 1).[1] The potential generality of the reaction is indicated by the results summarized in Table 1.

Despite a recent surge of publications on Ti(II)-promoted carbon−carbon bond formation involving alkenes, alkynes, and related heteroatom containing π-compounds,[2] those that are catalytic in Ti are rare, and such reactions appear to be limited to the enyne[3a,b] and alkenone[3c] bicyclization−isocyanide or CO insertion tandem process and the alkenone bicyclization−silane reduction tandem process[3d,e] catalyzed by titanocene derivatives. However, our attempts to cyclize 1-phenyl-6-hepten-1-yne with either EtMgBr in the presence of 10 mol % of Cp_2TiCl_2 or Et_2Zn in the presence of 10 mol % of Cp_2TiCl_2 and 20 mol % of Bu^nLi or EtMgBr led mostly to the formation of (*Z*)-1-phenyl-1,6-heptadiene after protonolysis. Thus, alkoxytitanium derivatives, i.e., $XTi(OPr^i)_3$, where X is Cl or OPr^i, appear to be especially suited for the observed cyclic carbozincation reaction. Other variations of the presently reported reaction have led to inferior results. Thus, replacement of Et_2Zn with 2.5 equiv of EtMgBr or Pr^iMgBr in the reaction of 1-(trimethylsilyl)-6-hepten-1-yne led to its consumption, but only complex mixtures resulted. Similarly, replacement of Et_2Zn with Et_3Al led to complex mixtures, even though a significant amount of the starting enyne remained unreacted. The use of EtZnI in place of Et_2Zn did not induce the desired cyclization, with the starting enynes remaining unreacted. Thus, Et_2Zn has thus far been essential to observing the desired clean cyclization in high yields. An alkylmagnesium derivative is also critically needed. Without it, the starting enyne remains unreacted. The use of Bu^nLi in place of EtMgBr led to low yields (20−30%) of the desired cyclization products with the balance of the starting enyne remaining unreacted. We earlier found that the same enyne could be cyclized to give the corresponding aluminabicycle in a moderate yield using Et_3Al and 10 mol % of Cp_2ZrCl_2,[4] but its scope appears to be much more limited. Very recently, a Ni-catalyzed organozinc-promoted carbocyclization of electron-deficient enynes was reported,[5] but it is clearly distinct from that reported herein.

Scheme 1



Although 2.5 equiv of Et_2Zn was used in most cases, it appears that only 1 equiv of Et_2Zn per enyne is necessary as indicated by entry 3 in Table 1. The results also indicate that there is only one Zn atom per enyne, although the exact structures of the organozinc products remain unclear beyond those represented by **2**. The need for an alkylmagnesium derivative strongly suggests Ti(II) derivatives, presumably alkene−Ti(II) complexes, as the active species, as in the stoichiometric versions.[2] Once they are generated, catalytic cycles must be sustained with enynes and Et_2Zn. Despite some ambiguities, the mechanism shown in Scheme 2 may be suggested.

Monoynes do undergo a related cyclization reaction, but it is a much slower reaction that needs to be further developed. Specifically, the reaction of 5-decyne with the standard reagent system consisting of 2.5 equiv of Et_2Zn, 10 mol % of $Ti(OPr^i)_4$, and 20 mol % of EtMgBr in Et_2O−hexanes slowly proceeded at 23 °C. After 24 h, the same quantity of $Ti(OPr^i)_4$ was added to drive the reaction to completion. After 4 d, the desired (*Z*)-5-ethyl-5-decene was obtained in 64% yield after protonolysis. Attempts to convert 1-phenyl-8-nonen-1-yne and 1-phenyl-5-hexen-1-yne into the desired seven- and four-membered ring products under the standard Ti−Mg-catalyzed carbozincation conditions resulted in mere ethylzincation as described above. Evidently, these enynes functioned as ordinary alkynes.

Although carbonylation of organozinc products has not been successful,[6] treatment with 1 equiv of CH_3OCH_2Br per enyne converted the organozinc derivatives to 1-alkenylbicyclo[*n*.1.0]-alkanes, where *n* is 3 or 4. The results may be interpreted as shown in Scheme 3. Thus, CH_3OCH_2Br must selectively react with the alkenyl−Zn bond to generate **8**, which must then undergo homoallyl−cyclopropylcarbinyl rearrangement and deoxyzincation to produce **6**.

The operational simplicity of the catalytic cyclization method herein reported can be seen in the following representative procedure for the conversion of **1** (Y = CH_2; Z = Ph) into the

---

[†] Most of the results were presented at the 9th IUPAC meeting on Organometallic Chemistry Directed toward Organic Synthesis (OMCOS 9), Göttingen, Germany, July 20−25, 1997.

(1) For some representative reviews on transition-metal-promoted and -catalyzed cyclization reactions of enynes and related compounds, see: (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: New York, 1991; Vol. 5, Chapter 9.1, p 1037. (b) Negishi, E. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: New York, 1991; Vol. 5, Chapter 9.5, p 1163. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(2) (a) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. (b) Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261. (c) Gao, Y.; Harada, K.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 5913. (d) Gao, Y.; Harada, K.; Sato, F. *Chem. Commun.* **1996**, 533. (e) Urabe, H.; Sato, F. *J. Org. Chem.* **1996**, *61*, 6756. (f) Gao, Y.; Shirai, M.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 7787.

(3) (a) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912; **1994**, *116*, 8593. (b) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. (c) Kabalaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818; **1997**, *119*, 4424. (d) Kabalaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785; **1996**, *118*, 3182. (e) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787.

(4) (a) Choueiry, D. Ph.D. Dissertation, Purdue University, 1995. (b) Negishi, E.; Montchamp, J. L.; Anastasia, L.; Elizarov, A.; Choueiry, D. *Tetrahedron Lett.* In press.

(5) Montgomery, J.; Oblinger, E.; Sawchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.

(6) Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732. For a recent cocatalyzed carbonylation of organozincs, see: Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 8411.

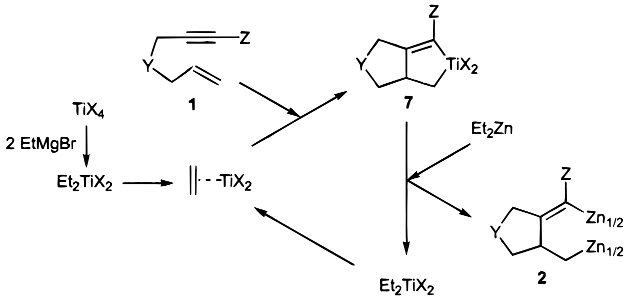
S0002-7863(97)03841-9 CCC: $15.00

Table 1. Carbozincation of Enynes Catalyzed by Titanium(IV) Alkoxides and Alkylmagnesium Derivatives[a]

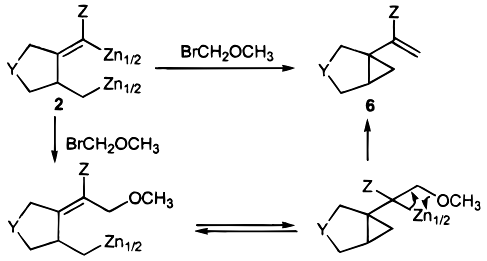
	enyne (**1**)					product yield,[b] %			
entry	Y	Z	X of $XTi(OPr^i)_3$	RMgX	time, h	**3**	**4**	**5**	**6**
1	CH_2	SiMe3	Cl	EtMgBr	3	85		53[c]	99
2	CH_2	SiMe3	OPr^i	Pr^iMgCl	42	84			
3	CH_2	Ph	Cl	EtMgBr[d]	3	93 (90)[c]	90[e]	61 (59)[c]	80 (61)[c]
4	CH_2	Me	Cl	EtMgBr	3	60		50	
5	O	Ph	Cl[f]	EtMgBr	48	95		95	
6	$(CH_2)_2$	$SiMe_3$	Cl	Pr^iMgCl	18	80			
7	$(CH_2)_2$	$SiMe_3$	Cl	EtMgBr	18	75			
8	$(CH_2)_2$	$SiMe_3$	OPr^i	Pr^iMgCl	48	89	79[g]		
9	$(CH_2)_2$	Ph	Cl	EtMgBr	24	83		56[c]	62
10	$(CH_2)_2$	Bu^n	Cl	EtMgBr	24	86			
11	CH_2O[h]	Me	Cl	EtMgBr	18	65			

[a] Unless otherwise mentioned, enynes were treated at 23 °C with 2.5 equiv of Et_2Zn, 10 mol % of $XTi(OPr^i)_3$, where X = Cl or OPr^i, and 20 mol % of an alkylmagnesium halide, EtMgBr and Pr^iMgBr, in Et_2O−hexanes. [b] Unless otherwise mentioned, the yields were determined by either GLC or NMR using appropriate internal standards. [c] Isolated yield. [d] Only 1 equiv of Et_2Zn was used. [e] The extents of D incorporation in the methyl and benzylidene groups were ≥99 and >86%, respectively. [f] After the reaction was run with 10 mol % of $ClTi(OPr^i)_3$ and 20 mol % of EtMgBr, for 24 h, an additional 10 mol % of $Ti(OPr^i)_4$ was added to complete the reaction. [g] The extents of D incorporation in the two labeled positions were ≥97%. [h] $MeC{\equiv}C(CH_2)_2OCH_2CH{=}CH_2$.

Scheme 2



Scheme 3



corresponding **5** and **6**. To a solution of 1-phenyl-6-hepten-1-yne (0.335 g, 2 mmol) and Et_2Zn (1 M in hexanes, 2 mL, 2 mmol) in ether (5 mL) and hexanes (3 mL) was added $ClTi(OPr^i)_3$ (0.5 M in hexanes, 0.4 mL, 0.2 mmol) followed by EtMgBr (3 M in Et_2O, 0.13 mL, 0.4 mmol). After 3.5 h at 23 °C, the reaction mixture was cooled to −78 °C, and a solution of I_2 (1.26 g, 5 mmol) in THF (10 mL) was added. The reaction mixture was warmed to 23 °C and stirred overnight. The mixture was then partitioned between 3 N aqueous HCl and ether. The organic layer was washed with water and aqueous $Na_2S_2O_3$. Drying over $MgSO_4$, concentration, and purification on silica gel (pentane) provided **5** (0.491 g, 1.15 mmol, 59%). The organozinc product **2** obtained as above was cooled to −78 °C, and freshly distilled $MeOCH_2Br$ (90%, 0.20 mL, 2.2 mmol) was added neat. The reaction mixture was warmed to 23 °C, stirred overnight, and poured into 3 N aqueous HCl and ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to a yellow oil. Purification by chromatography on silica gel (pentane) provided **6** (0.219 g, 1.19 mmol, 61%).

In summary, the novel trimetallic Zn−Ti−Mg reagent systems provide a means of devising cyclization of enynes (and simple alkynes) with catalytic quantities of Ti and Mg reagents, which is potentially attractive for use in conjunction with chiral ligands, and such studies are currently underway. In a more general sense, the catalytic reaction reported herein promises to represent a breakthrough for converting a large number of known stoichiometric reactions with Ti−Mg reagent systems[2] into catalytic processes.

Acknowledgment. We thank the National Science Foundation (CHE 9704994) for support of this research.

Supporting Information Available: Spectral data and elemental analyses of some representative products (22 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA973841N